News and Views from the Literature

Prostate Cancer

Early Hormonal Therapy for Prostate Cancer: The Good, the Bad, and the Ugly

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[*Rev Urol*. 2005;7(3):187-189]

Hormonal deprivation therapy has been the most avidly used treatment for advanced prostate cancer since its first description by Huggins and Hodges in 1941,[1] a discovery for which Dr. Huggins shared the Nobel Prize in Medicine in 1966. Since that time, great controversy has arisen regarding the optimal timing for the initiation of hormonal therapy. Today, because of prostate-specific antigen (PSA) screening and early detection, patients are diagnosed much earlier than in the past, resulting in a long natural history of disease before the development of metastasis or death. Indeed, among men with a biochemical failure after radical prostatectomy, the median time to developing metastasis is 8 years and the median time to death an additional 5 years.[2] Clearly, hormonal therapy can affect quality of life.[3] Therefore, within this context, when is the best time to begin hormonal therapy, and is that timing the same for all men? Two recently published articles shed light on which patients might benefit and which actually might be harmed from early hormonal therapy. Finally, a third article reminds us that hormonal therapy, although a very potent antitumor agent, exacts a cost.

Early Versus Delayed Hormonal Therapy for Prostate Specific Antigen Only Recurrence of Prostate Cancer After Radical Prostatectomy

Moul JW, Wu H, Sun L, et al.

J Urol. 2004;171:1141-1147.

The aim of this study was to determine whether androgen deprivation therapy (ADT) given early after a biochemical recurrence after radical prostatectomy delayed the development of metastatic disease relative to ADT given later in the disease course. To study this issue, Moul and colleagues relied on retrospective data from the large, multicenter Center for Prostate Disease Research database. This database contains data from multiple active military hospitals across the country. From this database, the investigators identified 1352 men who underwent radical prostatectomy during the PSA era and had a biochemical failure with at least 6 months of follow-up. These patients were the study subjects of this report.

Early hormonal therapy was defined by the PSA level at the time of initiation of ADT, with the investigators examining multiple definitions of "early hormones." In addition, to assess whether there were subsets of men in whom early treatment particularly affected outcome, men were risk stratified into low- and high-risk groups according to multiple definitions.

Interestingly, in this contemporary cohort of men with PSA failures, nearly 75% of men had not received ADT after a median follow-up of more than 4 years after

biochemical failure. Of those who did start hormonal therapy, the majority started at PSA levels between 0.25 and 2.5 ng/mL.

The 2 key findings from this study were that 1) among all men, the timing of hormonal therapy did not impact on the risk of developing metastatic disease; and 2) among men with high-risk disease (pathologic Gleason sum > 7 *and* a PSA doubling time ≤ 12 months), delayed hormonal therapy (starting when the PSA level was > 5 or > 10 ng/mL) was associated with an approximately 2-fold increased risk of metastasis.

Moul and colleagues discuss possible reasons for the lack of association with development of metastasis among all patients. Specifically, many men with low-risk disease will have a long indolent course, and therefore any secondary treatment is unlikely to show a benefit in a group of men with an extremely low risk of developing metastasis in the first place. However, the investigators are cautious to warn that this is a retrospective study, which requires validation. Despite these limitations, this study does suggest that at least in the short term (4 years after failure), hormonal therapy benefits only men with the highest-risk disease. Moreover, whether delaying the development of metastasis will translate into a survival advantage is as yet unknown.

Bicalutamide 150 mg in Addition to Standard Care in Patients with Localized or Locally Advanced Prostate Cancer: Results from the Second Analysis of the Early Prostate Cancer Program at Median Followup of 5.4 Years

Wirth MP, See WA, Mcleod DG, et al.

J Urol. 2004;172:1865-1870.

The hypothesis of this study was that bicalutamide would delay the time to clinical progression after definitive treatment or among men managed with watchful waiting. To assess this, Wirth and colleagues performed a review of data from 3 randomized, double-blind, placebo-controlled clinical trials of bicalutamide 150 mg daily versus placebo for men receiving standard care for prostate cancer (trials 23, 24, and 25). Standard care consisted of radical prostatectomy, radiation therapy, or watchful waiting. A total of 8113 men were randomized to bicalutamide (4052) or placebo (4061). The primary end points were progression-free survival and overall survival. Tolerability was a secondary end point. Median follow-up after randomization was 5.4 years. It should be noted that more details of trial 25 were published in the same issue of the *Journal of Urology*.[4]

Overall, bicalutamide therapy was associated with a 27% and 43% decreased risk of clinical progression relative to placebo in studies 24 and 25, respectively. However, in study 23, the only study that included patients from North America and in which no patients were managed with watchful waiting, bicalutamide provided little protection against clinical progression.

Whether data for the 3 studies were examined separately or combined for analysis, there was no statistically significant difference in overall survival between the bicalutamide and placebo groups. However, when the data from the 3 studies were combined and stratified by definitive treatment versus watchful waiting and stage of disease (local vs locally advanced), a very interesting observation was noted. Specifically, among men who received radical prostatectomy or radiation therapy, bicalutamide was not significantly related to overall survival, regardless of disease stage. When data from men who were managed with watchful waiting was examined, it was found that bicalutamide was associated with an improvement in overall survival (which did not reach statistical significance: hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.63-1.04; $P = .10$) among men with advanced disease, but a significantly worse overall (non–cancer-specific) survival among men with localized disease (HR 1.23; 95% CI 1.00-1.50; $P = .05$). Thus, men with advanced disease managed with watchful waiting were 19% *less* likely to die while receiving bicalutamide, whereas men with localized disease managed with watchful waiting and taking bicalutamide were 23% *more* likely to die.

It was unclear why bicalutamide was associated with an increased risk of death among men with localized disease managed with watchful waiting. Bicalutamide has known estrogenic effects, as demonstrated by the 73% incidence of breast pain and 68% incidence of gynecomastia seen in the bicalutamide arm. However, when the causes of death were examined, there did not seem to be an increase in cardiovascular deaths, as might have been predicted with an estrogenic compound.

Interestingly, the results of this trial somewhat mirror the results from the retrospective study by Moul and colleagues discussed above: early hormonal therapy might benefit men with high-risk/advanced disease but provides no benefit or might even harm men with low-risk/local disease. It is important to keep in mind that most men today will present with localized disease. Moreover, among men who do undergo treatment and have a biochemical

progression, most men will have low-risk recurrence (Gleason sum ≤ 7 or PSA doubling time at the time of recurrence > 12 months). Indeed, in the Moul and coworkers study, 75% of men with recurrences after radical prostatectomy had low-risk disease according to their definition. Therefore, these 2 studies suggest there might be a benefit for early hormonal therapy in some patients,

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though this is clearly the minority. Indeed, most patients, on the basis of these 2 studies, gained little benefit or might even have been harmed from early hormonal therapy. Moreover, the quality of life aspects, which were not extensively discussed in these 2 articles, further argue that ADT should be reserved for only truly high-risk men with advanced disease.

Risk of Fracture After Androgen Deprivation for Prostate Cancer

Shahinian VB, Kuo YF, Freeman JL, Goodwin JS.
N Engl J Med. 2005;352:154-164.

Shahinian and colleagues asked whether use of ADT affected the risk of developing a bone fracture and particularly a fracture that required hospitalization. The premise for this study was that prior studies have shown that hormone therapy has a negative impact on bone density. However, studies of the risk of fracture either were small or did not include a control group. Therefore, in the current study, the investigators used data from 50,613 men who received a diagnosis of prostate cancer in the period from 1992 through 1997 within the linked databases of the Surveillance, Epidemiology, and End Results program and Medicare. Patients who never received hormonal therapy were compared with men who received hormonal therapy within 6 months after diagnosis. A total of 31% of the study subjects received hormonal therapy.

Presumably, men who received hormonal therapy had more advanced disease, possibly metastatic to the bone before initiation of treatment. Consistent with that hypothesis, Shahinian and colleagues found that men who received hormonal therapy had an increased risk of fracture *before* receiving hormonal therapy, relative to men who never received hormonal therapy ($P = .01$). However, the absolute difference in the percentage of men who had a fracture was small (3.4% vs 2.8%).

After adjusting for baseline patient (eg, race, socioeconomic status, comorbidities) and cancer (eg, stage, grade) characteristics and degree of osteopenia at baseline, hormonal therapy was significantly related to increased risk of fracture. Moreover, there was a dose–response curve: men who received more doses of a gonadotropin-releasing hormone agonist were at higher risk. In addition, hormonal therapy was even more strongly associated with fracture requiring hospitalization than with fracture in general. Men who received an orchiectomy were 54% more likely to have a fracture and 70% more likely to require hospitalization for a fracture than men who did not receive ADT. Interestingly, the investigators found that hormonal therapy increased the risk of fracture most among younger and healthier men.

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In summary of the studies reviewed, it is becoming increasingly clear that early hormonal therapy might provide a significant benefit to a select group of high-risk men. Indeed, it is likely that these men, left untreated, would have progressed rapidly to metastasis, such that the added time receiving "early" hormonal therapy is likely small. However, there is also growing evidence that men with low-risk localized disease gain no benefit and might be harmed by hormonal therapy. Intuitively, these men are at low risk for progression or death from prostate cancer. Moreover, in considering the timing of hormonal therapy, especially given the long natural history of prostate cancer, one must consider not only the impact on survival but also the impact on quality of life. ■

References

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